

Decoding plant physiology through systems biology: Integrative multi-omics and computational perspectives for next-generation crop design

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ABSTRACT

The convergence of high-resolution multi-omics technologies with computational systems biology is transforming plant physiology by enabling predictive, mechanistic, and field-relevant insights into crop performance, adaptation, and resilience. This review presents an integrative and forward-looking synthesis spanning genomics, transcriptomics, proteomics, metabolomics, epigenomics, phenomics, and the rapidly emerging fields of single-cell and spatial omics, highlighting how these complementary layers can be computationally unified to achieve cell-type-resolved and tissue-specific insights into plant function. We discuss integrative analytical frameworks that combine gene regulatory network inference, machine learning, and explainable artificial intelligence (XAI), illustrating how these approaches accelerate the identification of key regulators, improve genotype–environment interaction modeling, and advance multiscale phenotypic prediction. Representative case studies demonstrate how multi-omics integration—ranging from single-cell transcriptomic atlases in *Arabidopsis* to nitrogen-use-efficiency modeling and omics-guided genome editing in cereals—bridges laboratory-scale discovery with field-level validation. We further propose a translational roadmap that links persistent bottlenecks, including data heterogeneity, limited spatiotemporal resolution, and the underrepresentation of non-model species, with actionable solutions such as FAIR-compliant data infrastructures, high-resolution spatiotemporal omics, hybrid mechanistic artificial intelligence (AI) modeling, and digital twin frameworks. By connecting molecular mechanisms to ecosystem-level performance, this review articulates a coherent vision for predictive, design-driven, and climate-resilient agriculture grounded in systems-level plant biology.

Key words: explainable AI, gene regulatory networks, multi-omics integration, predictive systems biology, single-cell and spatial omics, translational crop design

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INTRODUCTION

Plants, as sessile organisms, rely on intricately regulated molecular networks to coordinate growth, development, and adaptive responses to ever-changing environmental conditions. These networks arise from dynamic interactions among genes, proteins, metabolites, and environmental cues, forming multilayered systems that collectively govern plant physiology. Traditional molecular and reductionist approaches have identified critical genes and pathways, but they often fail to capture emergent properties arising from nonlinear feedback, network topology, and cross-scale interactions (Lephatsi et al., 2021; Zhang et al., 2025). As

agriculture confronts intensifying challenges driven by climate change, soil degradation, and rising global food demand, there is an urgent need for predictive and mechanistic frameworks that integrate molecular complexity with field-scale performance to accelerate rational crop design (Ali and Georgiev, 2023; Panotra et al., 2024; Khan, 2025).

The advent of high-throughput omics technologies—including genomics, transcriptomics, proteomics, metabolomics, epigenomics, phenomics, and rapidly advancing single-cell and spatial omics—has transformed plant biology by enabling quantitative interrogation of cellular, developmental, and physiological states

at unprecedented resolution (Lv et al., 2024; Fan et al., 2025). These multilayered datasets have uncovered novel regulators, dynamic gene–metabolite interactions, and cell-type- and tissue-specific stress responses (Ali and Alrashid, 2025; Wei et al., 2025). However, their scale, complexity, and heterogeneity necessitate advanced computational frameworks capable of coherent integration and interpretation across biological hierarchies and environmental contexts. Systems biology, which integrates multi-omics data with mathematical modeling and network-based inference, provides a unifying paradigm for decoding plant physiology in a holistic yet mechanistic manner (Koh et al., 2024; Roth et al., 2025; Yu et al., 2025). Beyond descriptive analyses, systems biology emphasizes prediction, causality, and hypothesis testing, thereby bridging molecular insights with actionable strategies for precision breeding and next-generation crop engineering (McCoy et al., 2021; Ali and Georgiev, 2023; Chen et al., 2025).

Recent advances underscore the transformative potential of such integrative approaches. For example, multi-omics studies in maize under nitrogen deficiency have identified transcriptional regulators and gene networks underlying nitrogen use efficiency, whereas single-cell transcriptomic analyses of *Arabidopsis* meristems resolved cell-type-specific signaling modules that control developmental plasticity (Zhang et al., 2019). Nevertheless, progress across crop species remains uneven. In cassava and millet, limited genomic resources and the absence of well-annotated pangenomes continue to constrain systems-level analyses, highlighting persistent disparities between model and non-model crops (Pazhamala et al., 2021; Varshney et al., 2021; Sehgal et al., 2024; Sanooja et al., 2025). Moreover, translating discovery from laboratory settings to field contexts is complicated by environmental heterogeneity, complex genotype–environment interactions, and the scarcity of robust multi-location validation pipelines (Cooper et al., 2016; Amin et al., 2025; Dai et al., 2025).

Non-model crops are particularly disadvantaged despite their agronomic and ecological importance. For example, multi-omics resources for cassava and millet lag substantially behind those available for major cereals, constraining the dissection of traits related to biotic stress resistance, drought resilience, and nutrient use efficiency (Ding et al., 2019; Pazhamala et al., 2021; Dai et al., 2025). Even in relatively data-rich species such as sorghum, field-level translation remains limited by the complexity of genotype–environment interactions, sensor–trait calibration drift, and the lack of standardized, FAIR-compliant data infrastructures that enable reproducible cross-site and cross-season analyses (Garcia-Oliveira et al., 2020; ISRFG, 2023; Mukherjee et al., 2024; Murray et al., 2025). To address these barriers, this review emphasizes field-validated case studies and standards-driven workflows that integrate single-cell and spatial insights with canopy-scale phenotyping and breeding pipelines. Overcoming these bottlenecks will require harmonized genomic resources, interoperable field-omics platforms, and FAIR-compliant infrastructures to ensure data transparency and reusability (Wilkinson et al., 2016; Dumschott et al., 2023; Baião et al., 2025).

At the computational frontier, advances in co-expression analyses and gene regulatory network (GRN) inference methods

(e.g., WGCNA and GENIE3) have facilitated functional dissection of molecular modules, while graph neural networks (GNNs) and explainable artificial intelligence (XAI) are increasingly delivering interpretable predictions for complex traits and environmental responses (Chowdhury et al., 2022; Chen et al., 2025; Pan et al., 2025; Wu and Xie, 2025). Case studies further highlight the translational power of these approaches: multi-omics integration has guided CRISPR–Cas9 editing of stress-resilient traits in rice and maize, and machine-learning-assisted phenomics has enabled early detection of nutrient imbalances and pathogen outbreaks under field conditions (Santosh Kumar et al., 2020; Farooq et al., 2024; Kaya, 2025; Mansoor et al., 2025).

Despite remarkable progress, several key challenges persist. Limitations in data standardization, reproducibility, and spatiotemporal resolution continue to constrain model robustness and predictive accuracy (Liu et al., 2024; Luo et al., 2024). Moreover, the translational impact of systems-level insights depends on effective alignment with breeding pipelines, regulatory frameworks, and socio-technical adoption pathways. Bridging molecular networks with field-scale phenotypes will therefore require not only advanced computational and modeling capabilities, but also coordinated validation across species, environments, and policy domains.

This review synthesizes recent advances in multi-omics integration, computational modeling, and translational systems biology, highlighting representative case studies in plant development and stress resilience. Collectively, these examples demonstrate that systems biology principles have moved beyond theory and are now being operationalized within field-validated, data-driven breeding pipelines. The review further examines the emerging roles of single-cell and spatial omics, evaluates the potential of artificial intelligence (AI)-enabled predictive frameworks, and explores translational applications ranging from genome editing to digital twin platforms for predictive agriculture. Finally, we propose a strategic roadmap that explicitly links current bottlenecks to actionable solutions, outlining how data-driven systems biology can accelerate next-generation crop design, enhance nitrogen use efficiency, and support climate-resilient agriculture for the 21st century.

MULTI-OMICS PLATFORMS: FROM BULK PROFILING TO SINGLE-CELL, SPATIAL, AND FIELD SCALES

Deciphering plant physiology requires the integration of molecular information across hierarchical layers, from genomes to phenomes. Classical bulk omics approaches—including genomics, transcriptomics, proteomics, metabolomics, epigenomics, and phenomics—have identified key regulators of development, metabolism, and stress adaptation (Fleury et al., 2010; Liao et al., 2019; Subramanian et al., 2020; Satrio et al., 2024; Varadharajan et al., 2025; Wei et al., 2025). However, bulk profiling often obscures cell-type heterogeneity and lacks spatiotemporal resolution, thereby limiting its translational utility. Recent advances in single-cell and spatial omics address these constraints, establishing systems-level frameworks that link molecular dynamics to whole-plant physiology and, ultimately, field performance (Loers and Vermeirssen, 2024; Yuan and Duren, 2025). The conceptual

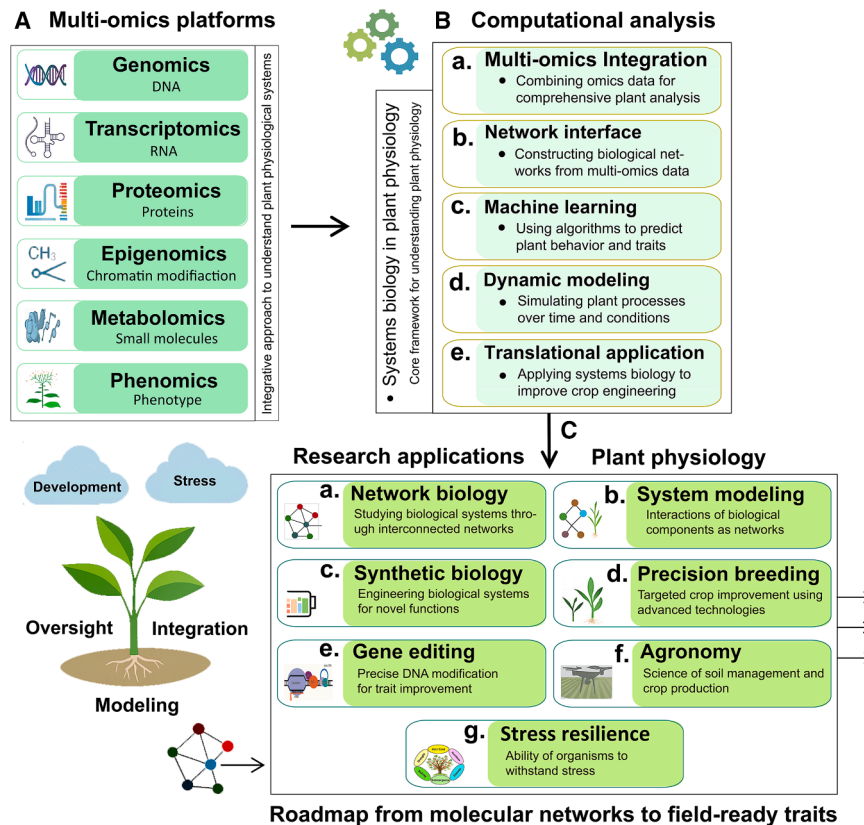


Figure 1. Systems biology roadmap linking multi-omics platforms, computational modeling, and translational crop design.

This schematic illustrates the predictive-to-translational continuum of plant systems biology through three integrated modules.

(A) *Multi-omics platforms*: genomics, transcriptomics, proteomics, metabolomics, epigenomics, and phenomics capture hierarchical biological regulation from molecular processes to phenotypic traits.

(B and C) (B) *Computational analysis*: multi-omics datasets are harmonized through data fusion, network inference, ML with explainable AI (XAI), and dynamic simulations of developmental and stress-responsive processes. (C) *Translational applications*: systems-level insights inform network and synthetic biology, genome editing, precision breeding, and agronomic validation. Together, these modules form an iterative feedback loop encompassing *omics acquisition, data integration, predictive modeling, and field deployment*. By incorporating single-cell and spatial omics for cell-type-resolved understanding, as well as digital twin frameworks for *in silico* phenotype forecasting, this roadmap delineates a coherent pathway from molecular networks to climate-resilient, data-driven crop systems, establishing systems biology as a predictive and translational foundation for next-generation agriculture.

integration of these multi-omics layers into a translational systems biology framework is summarized in Figure 1.

Genomes to single-cell and spatial omics

High-quality reference genomes and pangenomes for major crops such as rice, maize, and wheat, as well as for several orphan crops, now provide foundational frameworks for trait dissection, regulatory network reconstruction, and comparative genomics (Hu et al., 2025; Liu et al., 2025; MacNish et al., 2025). Complementing these resources, epigenomic maps of DNA methylation and histone modifications have revealed stress-induced chromatin plasticity; for example, drought-triggered DNA demethylation in maize and *Arabidopsis* is linked to enhanced stress tolerance (Schulze et al., 2021; Liu et al., 2022; Rao et al., 2024). Although bulk RNA sequencing (RNA-seq) remains central for identifying major regulators, single-cell RNA-seq (scRNA-seq) has uncovered extensive cellular heterogeneity and hormone-responsive transcriptional states in *Arabidopsis* and maize, including abscisic acid (ABA)-dependent regulatory hubs in guard cells under drought stress (Liu et al., 2023; Alrajeh et al., 2024; Lee et al., 2025). Integration of scRNA-seq with ATAC-seq and single-cell proteomics enables the reconstruction of cell-type-specific regulatory networks (Hu et al., 2023; Kumar Swain et al., 2025). Spatial transcriptomics and metabolomics further add positional context; for example, hormone and carbohydrate gradients in rice panicles delineate yield-associated zones, whereas spatial mapping of nitrogen remobilization in maize leaves reveals stress-responsive patterns (Wang et al., 2025a; Li et al., 2025). Collectively, these high-resolution omics layers bridge genome architecture with

physiology, forming the foundation for downstream GRN inference, explainable AI modeling, and digital-twin simulations. Cell-type-resolved GRNs reveal tissue-specific transcription factor–target interactions, while spatial co-variation refines causal priors, enhancing interpretability and target prioritization in predictive crop systems biology.

Metabolomics and biochemical networks

Metabolomics captures the biochemical outputs of regulatory networks shaped by genotype–environment interactions. In maize and rice, untargeted metabolomic profiling under nitrogen deficiency reveals coordinated trade-offs between primary carbon metabolism and secondary metabolite production, yielding biomarkers of nitrogen-use efficiency (Kundu et al., 2025b; Huang et al., 2025). Integrated transcriptome–metabolome analyses in sorghum further identify key transcription factors that orchestrate carbon–nitrogen balance (Murray et al., 2025), while drought-responsive metabolite signatures in cassava highlight pathways underlying stress adaptation (Ding et al., 2019; Sun et al., 2024b). Importantly, metabolomic markers are increasingly incorporated into predictive breeding pipelines, AI-driven trait prediction frameworks, and digital phenotyping platforms, transforming metabolomics from descriptive cataloging into a predictive component of systems biology (Cembrowska-Lech et al., 2023; Feng et al., 2024; Chen et al., 2025; Xu et al., 2025).

Phenomics and field-omics

Translating molecular discovery into agricultural innovation requires validation under field conditions. High-throughput

phenotyping platforms—including hyperspectral imaging, UAV-based sensing, and automated growth facilities—extend omics-derived predictions to canopy and population scales (Mansoor et al., 2025). For instance, hyperspectral indices integrated with transcriptomic data have accurately predicted canopy nitrogen status in rice, validating molecular regulators in real-world contexts (Takehisa et al., 2022; Jin et al., 2024; Kundu et al., 2025c). Multi-location field trials in sorghum and cassava further confirm the predictive value of omics-derived biomarkers for resilience-related traits (Garcia-Oliveira et al., 2020; Mukherjee et al., 2024). Collectively, these “field-omics” approaches bridge laboratory discovery with large-scale agronomic validation while generating datasets that feed into digital twins capable of simulating crop responses under variable climates (Fan et al., 2025).

Translational integration across scales

Together, these multi-omics platforms form a continuum from genome to phenotype, enabling integrative models that capture both molecular precision and environmental complexity. By layering single-cell and spatial omics with field phenomics, plant systems biology can (1) identify regulatory modules for genome editing and network rewiring, (2) discover biomarkers for stress-resilient breeding, and (3) construct digital twins capable of predicting crop performance across diverse environments (Yu et al., 2023; Fan et al., 2025). Unlike bulk-only approaches, this integrative framework directly links cellular heterogeneity to field-scale traits, accelerating the translation of systems biology from model species to underrepresented crops such as cassava, millet, and sorghum. In doing so, it addresses long-standing disparities in genomic resources and establishes systems biology as a driver of sustainable, climate-resilient agriculture (Pazhamala et al., 2021; Mukherjee et al., 2024; Satrio et al., 2024; Dai et al., 2025; Kutyauro et al., 2025). Phenomics–genomics integration now underpins trait-based selection in breeding, as summarized in Table 1. Together, Figure 1 and Table 1 establish the molecular-to-field continuum that supports the computational integration frameworks discussed in the following section.

COMPUTATIONAL APPROACHES BRIDGING OMICS AND PHYSIOLOGY

The growing complexity of plant systems necessitates computational frameworks that can integrate heterogeneous multi-omics datasets into predictive models that directly link molecular variation with physiology and field performance. While traditional descriptive analyses have provided valuable catalogs of genes and pathways, the transition toward *predictive and translational systems biology* is increasingly driven by advances in network inference, machine learning (ML), deep learning (DL), explainable AI (XAI), and mechanistic modeling (Ding et al., 2023; Zhang et al., 2023). These approaches not only reconstruct regulatory modules but also simulate dynamic processes and predict crop phenotypes under variable environments. Figure 2 illustrates this integrative framework, organized into five complementary pillars: (1) network biology and GRNs, (2) ML- and AI-based trait prediction, (3) integrative multi-omics modeling, (4) dynamic and mechanistic simulation, and (5) computational tools and resources. Graph-based data fusion and stacked multi-view learning unify transcriptomic, metabolomic, and phenomics layers for both network reconstruction and trait prediction (Chen et al., 2025).

Network biology and gene regulatory networks

Network biology provides a mechanistic foundation for linking molecular regulation to plant physiology by identifying key transcriptional modules and their upstream regulators. Methods such as weighted gene co-expression network analysis (WGCNA), GENIE3, and SCENIC enable GRN reconstruction from large transcriptomic datasets by correlating expression patterns and inferring transcription factor (TF)–target relationships (Aibar et al., 2017; Pan et al., 2025). Under nitrogen deficiency in maize, an integrated transcriptome–proteome–metabolome GRN revealed NLP7 and TCP transcription factors as master regulators of nitrogen-use efficiency, with WGCNA parameters optimized to preserve scale-free topology ($\beta \approx 12$; minimum module size ≈ 30) and module eigengenes showing strong correlations with root length and chlorophyll content (Fang et al., 2024; Zhang et al., 2024). In practice, hub ranking combines eigengene–trait associations, motif enrichment, and metabolite proximity, prioritizing transcription factors with high intramodular connectivity, conserved promoter motifs within 1 kb regions, and adjacency to nitrogen-diagnostic metabolites, thereby improving the efficiency of qPCR- and CRISPR-based validation. Similar GRN frameworks in *Arabidopsis* have uncovered ABA-responsive hubs governing drought adaptation (Aerts et al., 2024; Wang et al., 2024, 2025a; Fernández et al., 2025). Emerging single-cell and spatial transcriptomic technologies now enable GRN inference at cellular resolution, revealing meristematic and tissue-specific regulators that are obscured in bulk analyses (Loers and Vermeirssen, 2024; Yuan and Duren, 2025). Collectively, multi-scale GRN approaches quantitatively bridge transcriptional control and physiological function, thereby enhancing the predictive accuracy of stress-response and trait-modeling frameworks in plants.

Machine learning and trait prediction

ML has become integral to predictive plant systems biology by enabling quantitative mapping between molecular complexity and phenotypic performance. Classical supervised algorithms, such as random forests (RF) and support vector machines (SVMs), have successfully predicted drought tolerance in wheat and disease resistance in rice by integrating transcriptomic and metabolomic datasets (Galal et al., 2022). DL architectures, including convolutional neural networks (CNNs) and autoencoders, further expand predictive capacity for multi-omics integration and image-based phenomics. For example, in *Brassica*, transcriptome–metabolome integration using DL models accurately forecasts drought-responsive traits (Dublino and Ercolano, 2025). GNNs represent the next frontier by explicitly modeling biological interaction graphs, thereby capturing hierarchical dependencies across omics layers. In rice, GNNs that integrate transcript abundance, protein–protein interaction (PPI) networks, and phenotypic traits—such as tiller number and leaf nitrogen content—accurately predict yield components under variable nitrogen regimes (Wu and Xie, 2025). In practical multi-omics applications, GNNs are constructed with nodes representing genes (TPM/CPM expression values), proteins (spectral counts or DIA intensities), and metabolites (normalized peak areas). Edges encode curated PPIs, co-expression relationships, and enzyme–metabolite links, whereas graph-level readouts correspond to agronomic traits such as tiller number, canopy nitrogen status, or grain yield. Model interpretability is achieved through SHAP-based (SHapley Additive exPlanations) pathway-level attributions that quantify the

Omics platform	Primary targets	Core technologies	Key applications in plant physiology	Representative crops	References
Genomics	Genes, structural variants, genome architecture	Illumina, PacBio, Oxford Nanopore sequencing; pan-genomics; GWAS; CRISPR–Cas systems	Trait discovery, allelic variation analysis, genome editing, domestication gene mapping	Rice, maize, wheat, chickpea	Abbas et al. (2023) ; Mangal et al. (2024) ; Sun et al. (2024a) ; Kumar et al. (2025a)
Transcriptomics	mRNA, lncRNA, small RNAs, transcriptional dynamics	RNA-seq, single-cell RNA-seq, spatial transcriptomics, laser capture microdissection (LCM), CAGE-seq, microarrays	Developmental and stress-responsive gene expression, identification of stress-responsive TFs, alternative splicing analysis	<i>Arabidopsis</i> , maize, rice	Tohge et al. (2016) ; Hunt et al. (2023) ; Fan et al. (2025)
Proteomics	Protein abundance, post-translational modifications (PTMs), protein–protein interactions	Tandem MS (MS/MS), iTRAQ, TMT, data-independent acquisition (DIA), interactome profiling	Signal transduction, organellar proteomes, stress-regulated enzymes, phosphorylation cascades	Wheat, <i>Arabidopsis</i> , rice	Alrajeh et al. (2024) ; Liu et al. (2025)
Metabolomics	Primary and secondary metabolites, metabolic fluxes	GC–MS, LC–MS, CE–MS, NMR spectroscopy	Metabolic reprogramming under abiotic and biotic stress, pathway bottleneck identification, hormone–metabolite interactions	Tomato, rice, <i>Arabidopsis</i>	Tohge et al. (2016) ; Nakayasu et al. (2021) ; Alrajeh et al. (2024)
Epigenomics	DNA methylation, histone modifications, chromatin structure	Whole-genome bisulfite sequencing (WGBS), ChIP-seq, ATAC-seq, MNase-seq	Epigenetic memory, flowering regulation, stress priming, transposable element (TE) silencing, chromatin remodeling	<i>Arabidopsis</i> , soybean, wheat	Crisp et al. (2016) ; Wang et al. (2022) ; Li et al. (2024a) ; Chen et al. (2025)
Phenomics	Morphological, physiological, and developmental traits	UAV-based platforms, hyperspectral imaging, thermal/RGB sensors, fluorescence imaging, 3D scanning, chlorophyll fluorescence	High-throughput trait screening, early stress detection, phenotypic plasticity analysis, canopy architecture characterization	Rice, maize, barley	Gnädinger and Schmidhalter (2017) ; Hu et al. (2020) ; Kayess et al. (2024) ; Kundu et al. (2025b)
Multi-omics integration	Cross-layer molecular and phenotypic relationships	Co-expression networks, Bayesian inference, ML/DL models, multi-layer network modeling, canonical correlation analysis (CCA)	Predictive phenotyping, regulatory network reconstruction, trait-based breeding pipelines, gene–trait-association frameworks	Rice, maize, sorghum	Cembrowska-Lech et al. (2023) ; Sarfraz et al. (2025) ; Amin et al. (2025) ; Chen et al. (2025)

Table 1. Overview of omics platforms, their molecular targets, core technologies, and key applications in plant physiology. These frameworks synthesize multi-omics datasets into predictive models that link molecular regulation with plant physiology and trait performance.

contribution of individual molecular features to the predicted phenotype. This configuration enables multi-layer feature propagation and interpretable genotype–phenotype mapping in complex crops. Such AI-driven fusion frameworks increasingly employ graph-contrastive learning and cross-modal attention mechanisms to infer latent biological hierarchies beyond conventional correlation networks. Explainable AI (XAI) frameworks, such as SHAP, enhance model transparency and biological validity by identifying key regulatory modules and trait determinants, thereby facilitating

deployment in predictive breeding, genome editing, and decision-support pipelines ([Yang et al., 2022](#); [Koh et al., 2024](#); [Smeriglio et al., 2024](#)).

AI-powered multi-omics integration

AI-driven integration techniques are redefining systems biology by unifying multi-layered datasets. [Chen et al. \(2025\)](#) showed that deep autoencoders integrating transcriptomic and metabolomic

Computational approaches bridging omics and physiology

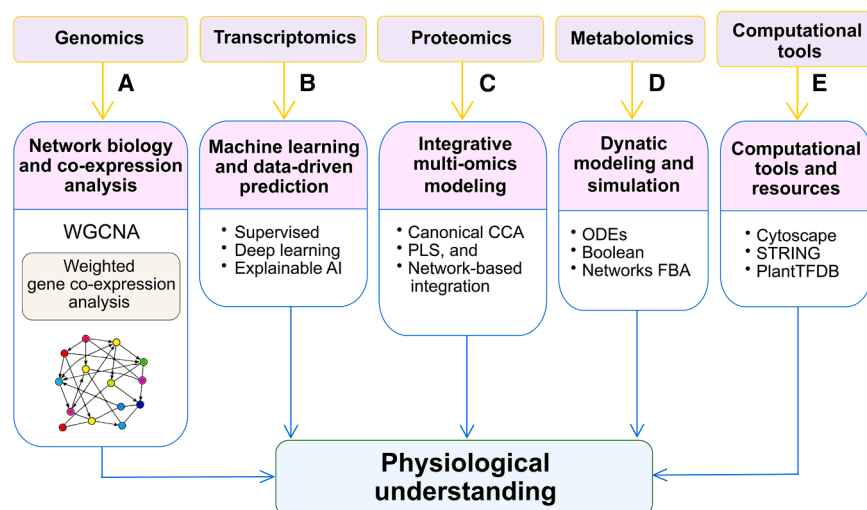


Figure 2. Computational frameworks integrating multi-omics data to predict plant physiological traits.

This conceptual model illustrates how diverse omics layers—including genomics, transcriptomics, proteomics, metabolomics, and phenomics—are integrated using advanced computational approaches to decode complex plant physiological traits. The framework is organized into five pillars.

(A) Network biology and co-expression analyses (e.g., WGCNA) identify trait-associated gene modules.

(B) ML and explainable AI enable pattern discovery and predictive modeling.

(C) Integrative multi-omics modeling leverages canonical correlation analysis (CCA), partial least squares (PLS), and network-based integration strategies.

(D and E) (D) Dynamic simulation approaches, including ordinary differential equations (ODEs), Boolean networks, and flux balance analysis

(FBA), model metabolic and developmental processes over time. (E) Computational tools and databases, such as Cytoscape, STRING, and PlantTFDB, support network visualization and regulatory inference. Collectively, these approaches translate high-dimensional molecular datasets into actionable physiological insights.

data across maize populations identified metabolic biomarkers associated with yield stability under drought. Similarly, multi-modal neural networks trained on combined genomic and phenomic datasets successfully predicted genotype $\times$ environment ($G \times E$) interactions in sorghum, directly linking molecular profiles with field-scale performance (Kutyauripo et al., 2025). Together, these studies illustrate how AI-powered models extend beyond classification toward network construction, trait discovery, and predictive breeding, with increasing application to underrepresented crops such as cassava and millet.

Dynamic and mechanistic modeling

Mechanistic approaches complement data-driven AI by enabling causal, time-resolved simulations of plant processes. Ordinary differential equation (ODE)-based models quantify the kinetics of transcriptional and hormonal signaling, Boolean networks capture binary regulatory switches, and flux balance analysis (FBA) predicts steady-state metabolic fluxes. Classic ODE-based models of auxin–crosstalk in *Arabidopsis* root meristems revealed emergent oscillatory dynamics that regulate stem cell maintenance (Muraro et al., 2014). In rice, FBA models of carbon–nitrogen allocation across vegetative and reproductive stages identified strategies to optimize yield and nitrogen-use efficiency, with validation from field data (Salon et al., 2017; Shameer et al., 2022). Integrating these mechanistic simulations with ML-based predictions yields hybrid virtual testbeds, enabling the *in silico* exploration of trait engineering and stress responses before costly field trials.

Computational tools and resources

The digital backbone of plant systems biology is built on specialized databases, analytical platforms, and reproducible workflows. STRING, ATTED-II, and PlaNet facilitate cross-species interaction mapping and network discovery (Szklarczyk et al., 2021). PlantRegMap and PlantTFDB enable transcription factor identification and promoter analysis (Jin et al., 2016; Tian et al., 2020). Cytoscape and GeneMANIA enable flexible network visualization

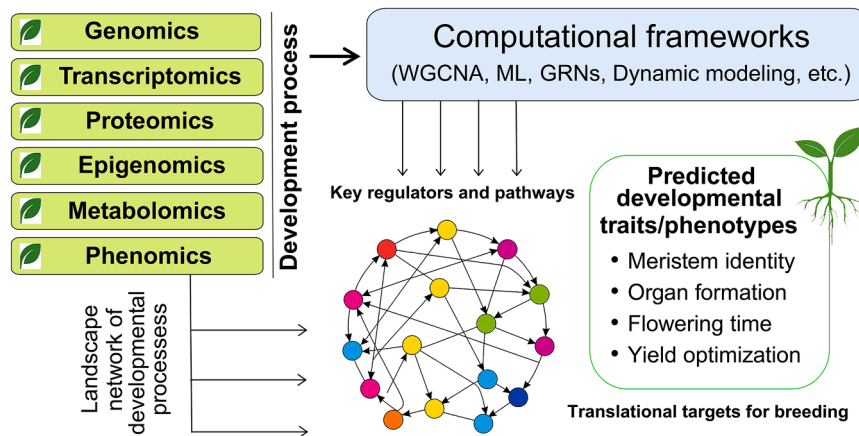
and analysis, whereas PaintOmics3, OmicsNet, and mixOmics provide pipelines for multi-omics integration (Singh et al., 2019; Shannon et al., 2023). Scalable workflow environments, such as Galaxy, KBase, and CyVerse, support FAIR-compliant, community-driven, and cloud-enabled research (Wilkinson et al., 2016; Heuckeroth et al., 2024; The Galaxy Community, 2024). Collectively, these tools ensure reproducibility, transparency, and accessibility, which are essential for translating plant systems biology into practical agricultural innovations.

Translational relevance

The convergence of GRN inference, ML/DL approaches, AI-powered integration, and mechanistic modeling underpins predictive frameworks essential for next-generation crop design (Zinati et al., 2024; Sarfraz et al., 2025). By linking omics-derived regulatory modules to field-level traits, these computational approaches enable (1) prioritization of candidate genes for genome editing, (2) rational design of synthetic metabolic pathways to enhance nutrient-use efficiency, and (3) construction of digital twins that simulate plant growth and stress responses under variable climates (Li et al., 2023; Fang et al., 2024; Kundu et al., 2025a; Amin et al., 2025). Importantly, these strategies extend predictive systems biology beyond model crops to non-model and orphan species, directly addressing disparities noted by reviewers and advancing the global agenda for sustainable, climate-resilient agriculture.

SYSTEMS BIOLOGY OF PLANT DEVELOPMENT

Plant development is orchestrated by tightly regulated genetic, epigenetic, and biochemical programs that integrate endogenous cues with environmental signals. Systems biology approaches enable the dissection of these developmental processes across cellular, tissue-specific, and temporal scales (Wang et al., 2022; Hemenway and Gehring, 2023; Catoni et al., 2025). This section



Decoding plant development processes by integrating multi-omics layers

strategies, including genome editing, synthetic circuit design, and ideotype optimization. Collectively, this framework links multi-omics insights to phenotypic plasticity, providing a mechanistic basis for predictive crop design.

integrates organ-level insights with computational and omics-based frameworks, illustrating how systems-level analyses elucidate the molecular logic underlying meristem function, organ patterning, flowering, hormone signaling, and developmental robustness (McCoy et al., 2021; Li et al., 2024b; Bulle et al., 2025).

Meristem maintenance and organogenesis

Shoot and root apical meristems (SAM and RAM) serve as centers of indeterminate growth. GRNs involving WUSCHEL (WUS), CLAVATA (CLV), and KNOX genes coordinate SAM maintenance and stem cell identity (Agarwal et al., 2022; Lindsay et al., 2024). In *Arabidopsis*, scRNA-seq coupled with GRN inference has revealed meristematic zonation and cell type-specific regulators (Ferrari et al., 2022; Cao et al., 2023). Similar approaches in maize and rice have elucidated RAM organization and lateral root development (Lindsay et al., 2024). Integrative proteomic and phosphoproteomic studies further highlight post-translational regulation of meristem activity, particularly in response to auxin-cytokinin gradients (Yu et al., 2021; Artur, 2023; Jain and Schmidt, 2024). In parallel, dynamic models simulate stem cell feedback regulation and positional signaling within the root meristem (Muraro et al., 2014). A predictive systems biology framework for decoding plant development and accelerating trait design is illustrated in Figure 3.

Leaf and floral organ patterning

Leaf and floral organ development is governed by spatial patterning mechanisms orchestrated by polarity genes, auxin transporters, and transcription factors. Time-series transcriptomic analyses have revealed coordinated expression of *ASYMMETRIC LEAVES1* (AS1), *YABBY*, and *KANADI* gene families during leaf polarity establishment (Báez, 2024). Epigenomic profiling has demonstrated a central role for the repressive histone mark H3K27me3 in maintaining organ identity (Liu et al., 2023; Lu et al., 2024). Floral organ identity specification is controlled by MADS-box-centered GRNs (Yan et al., 2016; Castañón-Suárez et al., 2024). In addition, integrative DNA methylome and ATAC-seq analyses reveal extensive epigenetic reprogramming during the floral transition (Tsuji and Sato, 2024; Xue et al., 2025).

Figure 3. Decoding plant developmental processes through integrative multi-omics analyses.

This schematic illustrates how integrative systems biology deciphers the regulatory logic underlying plant development through the convergence of multi-omics data and computational modeling. Genomic, transcriptomic, proteomic, metabolomic, and epigenomic layers are integrated using co-expression analysis, gene regulatory network (GRN) inference, ML, and dynamic modeling to reconstruct the molecular architecture underlying developmental processes. These frameworks identify key regulators, signaling nodes, and pathway interactions that coordinate meristem identity, organ patterning, flowering control, and yield formation. The inferred regulatory modules are further coupled with phenotypic datasets to enable predictive modeling of developmental outcomes and to guide translational

Recent computational modeling frameworks that integrate multi-omics datasets now enable simulation of flowering regulation and identification of key regulatory hubs (Zeng et al., 2020; Chien et al., 2023; Wang et al., 2023; Li et al., 2024a).

Flowering time and vernalization

Flowering is regulated by light, temperature, and developmental cues. Transcriptomic studies have identified the *CONSTANS-FLORING LOCUS T* (CO-FT) module as a central regulator of photoperiodic flowering (Vicentini et al., 2023; Li et al., 2024a). Epigenomic and RNA-seq analyses of FLC mutants in *Arabidopsis* have elucidated the vernalization pathway mediated by Polycomb-dependent transcriptional silencing (Wang et al., 2023). Mathematical models further capture epigenetic memory and flowering-time variation (Mahmood et al., 2024; Maple et al., 2024). These frameworks have been extended to cereal crops, where VRN1/VRN2 regulate vernalization responses and heading date (Wang et al., 2023; Sehgal et al., 2024).

Hormonal crosstalk and developmental integration

Multi-omics studies have revealed the complexity of hormone signaling networks. Auxin- and cytokinin-responsive modules regulate cell division, elongation, and organogenesis (Kolachevskaya et al., 2021; Ma et al., 2024b). In *Arabidopsis*, auxin-induced transcriptomic shifts are accompanied by coordinated proteomic and metabolomic reprogramming during root growth (Tohge et al., 2016; Zhang et al., 2023). Network analyses further reveal hormone crosstalk modules that integrate BR-ABA interactions via transcription factors such as BES1 and ABI5 (Koh et al., 2024). ML applied to hormone-responsive transcriptomes has enabled the prediction of previously unrecognized developmental regulators.

INTEGRATING OMICS FOR DEVELOPMENTAL MODELING

Multi-omics-based models simulate gene and network dynamics across developmental processes. Bayesian and Boolean models

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capture regulatory control in meristems and during the floral transition (Kazwini and Sanguinetti, 2024). Spatial simulations of auxin transport reproduce phyllotactic and vascular patterning. In rice and wheat, integrative transcriptome–QTL analyses have identified gene hubs governing plant architecture and yield-related traits (Tohge et al., 2016; Zhang et al., 2021b). Collectively, these predictive frameworks inform genomic selection and targeted breeding strategies aimed at optimizing developmental outcomes.

Overall, developmental systems biology integrates molecular, spatial, and dynamic data to elucidate the emergence of complex plant architectures and reproductive traits. These approaches bridge fundamental biological insights with translational crop improvement. The following section (Supplemental Tables 1 and 3) explores how similar strategies are applied to plant stress responses.

SYSTEMS BIOLOGY OF PLANT STRESS RESPONSES

Plants are continuously exposed to a wide range of abiotic and biotic stresses, including drought, salinity, extreme temperatures, nutrient imbalances, and pathogen attack. These stressors disrupt cellular homeostasis, reduce photosynthetic efficiency, and impair growth, ultimately threatening global food security (Ceulemans et al., 2021; Jiang et al., 2025). Systems biology has become indispensable for deciphering multilayered plant stress responses by integrating omics datasets, regulatory modeling, and physiological profiling. Supplemental Tables 2 and 3 summarize how diverse omics layers have been integrated across plant species to dissect stress-response mechanisms.

Multi-omics integration and regulatory reprogramming

High-throughput omics analyses have revealed extensive stress-induced reprogramming mediated by the DREB, WRKY, NAC, and MYB transcription factors (Wang et al., 2022; Yang et al., 2023; Panahi and Hamid, 2025). These regulators modulate stress-responsive gene clusters associated with osmoprotection, ROS detoxification, and metabolic reconfiguration. Time-series transcriptomic analyses and co-expression network modeling further resolve the temporal dynamics of stress responses, distinguishing early signaling cascades from later metabolic adjustments (Ncama et al., 2021; Mushtaq et al., 2025).

Proteomic and phosphoproteomic studies have uncovered stress-specific post-translational modifications (PTMs), including activation of SnRK2 kinases and MAPKs, which regulate ABA signaling, ion transport, and stomatal closure (Yin et al., 2021; Artur, 2023; Jardim-Messeder et al., 2025). Metabolomic profiling further reveals stress-induced accumulation of compatible solutes (e.g., proline and trehalose), antioxidants (e.g., ascorbate and glutathione), and specialized metabolites (e.g., flavonoids), indicating tight coordination between transcriptional regulation and metabolic adaptation (Tohge et al., 2016; Nepfali et al., 2020; Wani et al., 2021; Hina et al., 2024; Hasnu et al., 2025).

Epigenomic studies have identified dynamic changes in DNA methylation, histone acetylation, and chromatin accessibility at

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key promoter regions. These epigenetic reprogramming events support both short-term transcriptional plasticity and the establishment of long-term stress memory (Gallusci et al., 2023; He et al., 2024a, 2024b; Rao et al., 2024; Sena et al., 2024; Miryeganeh, 2025; Bendrihem et al., 2025).

Biotic stress responses and immune signaling networks

Transcriptomic and proteomic profiling of plant–pathogen interactions captures distinct defense phases, including pattern-triggered immunity (PTI) and effector-triggered immunity (ETI) (Pandey et al., 2023). Immune network reconstruction across species has identified conserved signaling hubs such as WRKY33, NPR1, EDS1, and PAD4, which modulate SA, JA, and ethylene pathways (Zhou and Zhang, 2020). Metabolomic analyses under pathogen attack reveal accumulation of defense-associated phytoalexins, glucosinolates, and antimicrobial flavonoids. Integrated omics analyses have further modeled growth–defense trade-offs, uncovering transcriptional compensation strategies during immune activation (Muñoz-Hoyos and Stam, 2023; Serag et al., 2023; Rahman et al., 2024). In parallel, proteomics-based interactomics has identified NLR–effector complexes and decoy proteins that mediate recognition and signaling specificity, providing a foundation for breeding broad-spectrum disease resistance (Kourelis and van der Hooft, 2018; Elmore et al., 2021).

Redox regulation and ROS signaling networks

Reactive oxygen species (ROS) act as both second messengers and damaging agents. ROS-responsive transcriptomes reveal regulatory networks involving RBOHs, GSTs, peroxidases, and NADPH oxidases (Sirko et al., 2021; Mittler et al., 2022; Rehman et al., 2023; Kundu et al., 2025a). Modeling of antioxidant pathways, such as the ascorbate–glutathione cycle and thioredoxin–peroxiredoxin systems, elucidates redox buffering under fluctuating stress conditions (Bendou, 2025; Kiliç et al., 2025). Kinetic models further demonstrate how ROS thresholds distinguish reversible signaling from irreversible damage and cell death (Foyer and Kunert, 2024). Redox enzymes, including NAD kinases (NADKs), balance NADP⁺/NADPH ratios, thereby linking energy metabolism to ROS homeostasis (Kračun et al., 2025; Lu et al., 2025). These insights have enabled redox-targeted trait selection in oxidative stress breeding.

Hormonal crosstalk and stress network integration

Multi-omics profiling of hormone signaling identifies central regulatory hubs, such as MYC2 (ABA–JA), WRKY70 (JA–SA), and EIN3 (ethylene), that mediate crosstalk under concurrent stresses (Jardim-Messeder et al., 2025). Simulation of hormonal fluxes and downstream transcriptional responses supports quantitative modeling of prioritization trade-offs in complex environments (Newman et al., 2023; Pandey et al., 2023). Dynamic interaction networks and feedback loops revealed through transcriptome–metabolome integration further highlight tissue-specific coordination of stress adaptation. Collectively, these systems-level models guide rational manipulation of hormonal balance to enhance stress resilience (Tan et al., 2022).

Translational applications: Toward climate-smart crops

Systems biology insights have enabled targeted genome editing of key regulatory genes such as *DREB2A*, *NAC72*, *RBOHF*, and

CAT1 in rice, tomato, and wheat, thereby conferring enhanced tolerance to drought, salinity, and oxidative stress (Santosh Kumar et al., 2020; Shelake et al., 2022). Marker-assisted selection informed by omics-derived biomarkers is advancing predictive breeding under field conditions. High-throughput phenotyping integrated with multi-omics approaches (field phenomics) further enables spatiotemporal monitoring of stress-related traits and genotype–environment interactions (Araus et al., 2018; Serag et al., 2023; Sun et al., 2024a; Pradhan et al., 2024). These tools are accelerating the development of climate-smart cultivars optimized for water-limited, high-salinity, and pathogen-rich agroecosystems.

Overall, systems biology reveals the multilayered nature of plant stress adaptation by integrating transcriptional regulation, redox dynamics, signaling crosstalk, and epigenetic memory. These integrative frameworks provide an essential foundation for breeding resilient crops capable of withstanding future environmental uncertainties.

TRANSLATIONAL SYSTEMS BIOLOGY AND CROP ENGINEERING

The convergence of systems biology, synthetic biology, and data-driven modeling has ushered in a new era of crop improvement (Benevenuto et al., 2022). Integrative multi-omics approaches, when coupled with advanced genome editing and high-throughput phenotyping platforms, enable the rational design of climate-resilient, nutrient-efficient, and high-yielding cultivars (Svitashev et al., 2016; Singh et al., 2022; Kitashova et al., 2023). By bridging fundamental discovery with applied breeding and biotechnology pipelines, translational systems biology offers scalable solutions to global food security and environmental sustainability challenges (Benevenuto et al., 2022; Artur, 2023; Roychowdhury et al., 2023; Sarfraz et al., 2025).

Genome editing guided by systems-level insights

Systems biology identifies candidate genes, regulatory hubs, and feedback circuits that serve as precision targets for genome editing tools such as CRISPR/Cas9, Cas12a, and base editors. Editing transcription factors (e.g., DREB2A, NACs, and bZIPs), stress sensors, and metabolic enzymes has enhanced tolerance to drought, heat, salinity, and pathogens (Zhang et al., 2021a; Abbas et al., 2023; Ma et al., 2024a). Regulatory circuit tuning through promoter engineering or multiplexed editing enables precise modulation of gene expression while minimizing fitness penalties (Shelake et al., 2022; Wu et al., 2024). Model-informed editing has been used to simulate gene knockouts or overexpression scenarios, predict trait outcomes, and reduce off-target effects. Tools such as GRN inference (e.g., GENIE3), flux balance analysis (FBA), and explainable AI models (e.g., SHAP, LIME) further support target prioritization for multiplexed trait stacking (Svitashev et al., 2016; Hunt et al., 2023; Koh et al., 2024). Recent examples include CRISPR/Cas-mediated stacking of *OsDREB2A*, *OsNAC6*, and *OsPYL4* in rice, which confers combined drought and heat tolerance and enhanced ABA signaling without growth penalties (Zhang et al., 2021a; Abbas et al., 2023; Jardim-Messeder et al., 2025). Similar stacking strategies are under development in tomato and wheat to

simultaneously improve root vigor, water-use efficiency, and disease resistance (Li et al., 2022).

Multi-omics in breeding and selection

The incorporation of transcriptomic, proteomic, and metabolomic markers into breeding programs enhances selection accuracy and efficiency (Sinha et al., 2021; Somegowda et al., 2024). Omics-assisted breeding accelerates the identification of genotype–phenotype associations, quantitative trait loci (QTLs), and expression QTLs (eQTLs) under stress conditions. For example, metabolite QTL (mQTL) mapping of osmolytes, antioxidants, and amino acids has enabled the identification of biochemical traits linked to stress tolerance and yield (Fleury et al., 2010). In maize, the co-localization of mQTLs with transcriptomic data has been used to identify elite lines with improved nitrogen-use efficiency and drought resilience (Kitashova et al., 2023). In soybean, transcriptome-guided genomic selection is being applied to pyramid traits for salinity tolerance and *Phytophthora* resistance (Vargas-Almendra et al., 2024). Genome-wide association study (GWAS) tools such as GEMMA, TASSEL, and PLINK support association mapping, whereas true multi-omics integration relies on frameworks such as mixOmics/DIABLO, MOFA, and network-based data fusion (Bradbury et al., 2007; Chen et al., 2016; Brouckaert et al., 2023).

Precision phenomics and trait prediction

Remote sensing, image-based phenotyping, and field-deployable sensors enable non-invasive monitoring of morphological, physiological, and biochemical traits. When integrated with multi-omics data, these phenomics platforms provide real-time insights into plant responses. ML models trained on integrated datasets can predict traits such as drought recovery, nitrogen-use efficiency, and disease severity (Angidi et al., 2025; Fatima et al., 2025; He et al., 2025). DL approaches and GNNs further infer trait correlations, genotype-by-environment interactions, and cell-level phenotypic plasticity. These approaches are now being applied in maize and sorghum breeding trials across sub-Saharan Africa (Dalton, 2022; Fernandes et al., 2024). In such frameworks, transcript, protein, and metabolite profiles serve as input features, network edges encode PPI and co-expression relationships, and outputs include trait predictions such as yield and nitrogen-use efficiency. Explainability layers (e.g., SHAP and integrated gradients) enable pathway-level feature attribution, facilitating downstream experimental validation (Koh et al., 2024).

Synthetic biology and modular design

Synthetic biology complements systems-level approaches by enabling the de novo design of genetic circuits and metabolic pathways. Modular components—including synthetic promoters, transcriptional switches, and inducible expression systems—can be rationally assembled to control developmental timing, metabolite flux, and hormonal balance. Representative examples include nitrate-inducible synthetic root circuits that reprogram branching architecture in response to nitrogen availability in *Arabidopsis* and rice (Kundu et al., 2025c; Kambampati et al., 2025), as well as RNA-based biosensors used to dynamically regulate salinity-responsive genes in tomato (Pray et al., 2011; Müller et al., 2025). Synthetic regulatory switches, such as logic-gated transcriptional circuits, have been deployed in *Nicotiana benthamiana* for conditional gene

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activation (Yasmeen et al., 2023). Engineering synthetic transcription factors with programmable DNA-binding domains, such as TALEs and CRISPRa, further expands the regulatory toolbox (Zhang et al., 2021a; Abbas et al., 2023). In rice, ongoing efforts aim to construct synthetic transcription factors that modulate flowering time and tillering in response to photoperiodic cues (Eguen et al., 2020; Shim and Jang, 2020; Gu et al., 2022).

Toward predictive and resilient agriculture

The integration of systems biology, phenomics, and precision breeding is transforming modern agriculture (Mansoor et al., 2025; Nautiyal et al., 2025). Predictive frameworks that model gene–environment interactions are increasingly used to simulate trait plasticity, optimize crop ideotypes, and inform planting decisions across variable climatic regimes. Collaborative initiatives such as the International Plant Phenotyping Network (IPPN; <https://www.plant-phenotyping.org>) (Tardieu et al., 2017), Crops *in Silico* (<https://cropsinsilico.org>) (Marshall-Colon et al., 2017), and the CGIAR Genebank Platform (<https://www.cgiar.org/initiative/genebank-platform/>) are deploying open-access tools, interoperable data pipelines, and simulation platforms to support global breeding programs. Collectively, these initiatives serve both smallholder and industrial agriculture in meeting food security targets under increasing climate uncertainty. Nevertheless, broad feasibility depends on rigorous validation beyond controlled environments. Multi-location trials in sorghum and cassava demonstrate that omics-derived biomarkers can anticipate resilience phenotypes, while canopy hyperspectral indices integrated with transcriptomic data accurately predict nitrogen status in rice under field conditions (Takehisa et al., 2022; Mukherjee et al., 2024). For instance, omics-based canopy nitrogen models achieved $R^2 > 0.8$ with RMSE < 5% in rice field validations (Jin et al., 2024). To ensure responsible deployment, several policy and implementation considerations are critical: (1) transparent AI model documentation and versioning; (2) rigorous biosafety evaluation of genome-edited lines; (3) FAIR (Findable, Accessible, Interoperable, Reusable) data licensing with persistent identifiers; and (4) the establishment of breeder–farmer data cooperatives to extend applications to non-model crops. Advancing commercial deployment further requires robust data governance and biosafety frameworks that emphasize transparent model reporting, breeder-friendly decision-support dashboards, and alignment with existing regulatory standards for genome editing and data privacy (Domingo, 2025; Mundorf et al., 2025). Collectively, these integrative and governance-oriented strategies strengthen the translational bridge from controlled experimental systems to global field environments, accelerating the realization of predictive, climate-resilient agriculture.

Future perspectives

Despite recent advances, challenges remain, including limited model transferability across genotypes and environments, regulatory acceptance of synthetic biological constructs, and data harmonization across heterogeneous phenotyping platforms. Future translational pipelines are likely to incorporate crop digital twins, edge computing for in-field analytics, and federated learning frameworks for multi-environment data sharing (Artur, 2023; Sanooja et al., 2025). Convergence with biodesign automation and cloud-connected laboratories could further

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accelerate iterative testing and deployment of engineered traits in near real time, representing a transformative leap in crop design (Sun et al., 2024a; Sarkar et al., 2024).

Together, translational systems biology is reshaping how crops are designed, evaluated, and optimized, as illustrated in Figure 4. By integrating omics-informed models, genome engineering, synthetic biology, and predictive analytics, researchers are developing resilient and productive cultivars tailored to future agroecological realities and global food security needs.

CURRENT CHALLENGES AND LIMITATIONS

Despite substantial advances in multi-omics and systems biology, the large-scale implementation and translational impact of these approaches in plant science remain limited. Key challenges—ranging from data heterogeneity and modeling complexity to insufficient field-level validation—continue to constrain the development of predictive, scalable, and actionable models (Yang et al., 2020). Addressing these bottlenecks is essential for bridging the gap between molecular discovery and practical agricultural innovation (Nakayasu et al., 2021; Artur, 2023; Pandey et al., 2023). Each of these challenges directly informs the strategic roadmap outlined below, in which targeted solutions are mapped to their corresponding limitations.

Data integration and standardization

The integration of systems biology datasets, often generated across different platforms, protocols, and time points, presents a major challenge in systems-level plant biology. These datasets differ substantially in dynamic range, resolution, and noise profiles, complicating cross-layer alignment and biological interpretation (Ye et al., 2020; Xu et al., 2022; Jamshidi et al., 2025; Sarfraz et al., 2025). Additionally, metadata inconsistencies, batch effects, and incompatible data formats hinder reproducibility and comparative analyses. Efforts to standardize data reporting and formatting—such as MIAME (for microarrays), MIAPE (for proteomics), and structured data formats including mzML, HDF5, and JSON-LD—are gradually being adopted to improve data integrity and interoperability (Leipzig et al., 2021; Abram and McCloskey, 2022). Ontology-based frameworks incorporating Plant Ontology, Gene Ontology, and environmental metadata schemas are also essential for harmonized data integration (Dumschott et al., 2023). Resources such as PLAZA, Gramene, ePlant, and PlantReactome, operating under FAIR (findable, accessible, interoperable, reusable) principles, are facilitating broader access to curated datasets (Arshinoff et al., 2022). Nevertheless, fully automated, scalable, and user-friendly data integration pipelines remain limited, especially for non-model crops. There is a critical need for robust, unified frameworks capable of handling complex, asynchronous, and multi-source omics data to support reproducible systems modeling (solution tags: pillars 1, 3, and 5 [hybrid modeling, XAI/causal inference, and field-omics integration]; Figure 6).

Temporal and spatial resolution limitations

Bulk omics approaches often obscure spatial, developmental, and cell-type-specific regulatory variation, which is essential for understanding dynamic physiological processes. Recent

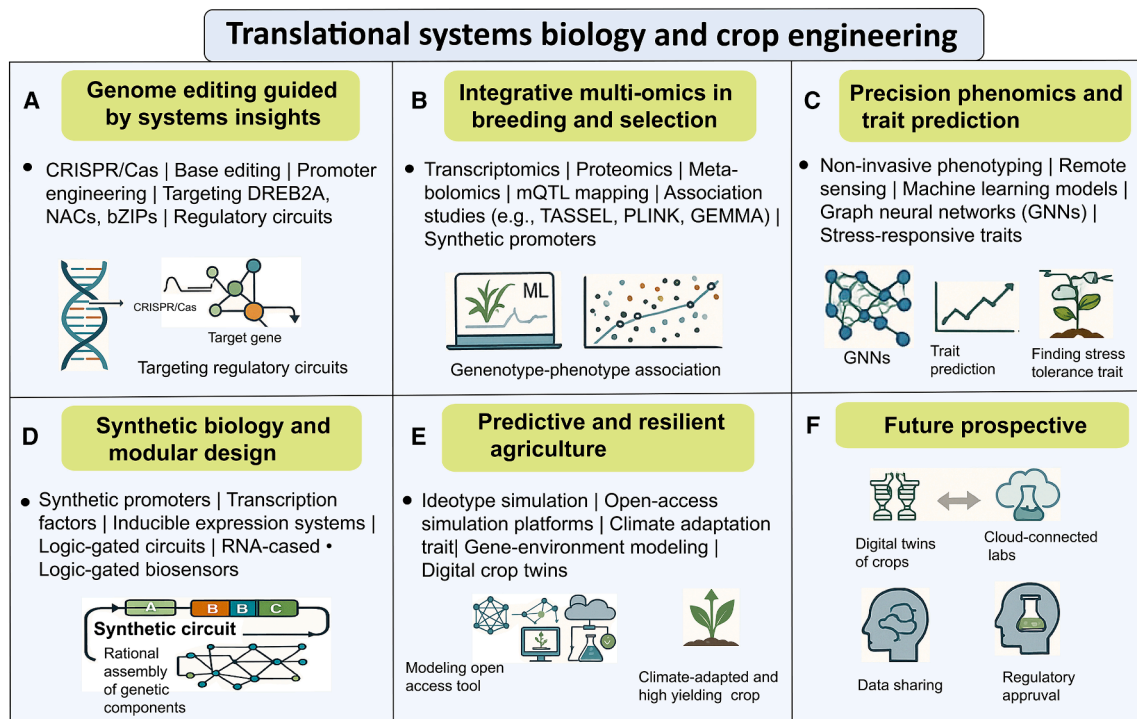


Figure 4. Translational systems biology framework for next-generation crop engineering.

This conceptual framework outlines six integrative pillars of translational systems biology that drive modern crop engineering.

(A) Systems-guided genome editing leverages regulatory network information to target key transcription factors (e.g., DREB2A, NAC family members, and bZIPs) using CRISPR/Cas technologies, base editing, and promoter engineering.

(B) Integrative multi-omics-enabled breeding and selection combine transcriptomic, proteomic, metabolomic, and association-mapping datasets (e.g., mQTL and GWAS) with ML to resolve genotype–phenotype relationships.

(C) Precision phenomics and trait prediction employ non-invasive imaging, remote sensing, and graph neural networks (GNNs) to predict complex traits under stress conditions.

(D) Synthetic biology and modular design enable the construction of synthetic promoters, logic-gated biosensors, and inducible transcriptional circuits.

(E) Predictive and resilient agriculture integrates ideotype modeling, digital crop twins, and climate-adaptation simulations.

(F) Future prospects include cloud-connected laboratories, streamlined regulatory pathways for synthetic biology applications, and open-access digital infrastructures that facilitate data sharing. Together, these strategies support the rational design of resilient, high-yielding, and climate-smart crops.

advances in scRNA-seq, spatial transcriptomics, and spatial metabolomics are beginning to address these limitations (Cuperus, 2022; Hunt et al., 2023; Wang et al., 2025b). Nevertheless, isolating viable plant cells for single-cell analyses remains technically challenging due to rigid cell walls, tissue-specific autofluorescence, and variability in enzymatic digestion efficiency (Ming et al., 2025). In addition, many omics studies are conducted under controlled or laboratory conditions, limiting their relevance to real-world agroecological variability. Capturing realistic physiological responses therefore requires the integration of time-series omics with field-based phenotyping and high-resolution environmental metadata (Araus et al., 2018; Kaur et al., 2021; Kumar et al., 2025b). There is a pressing need for scalable spatiotemporal multi-omics platforms that are tightly integrated with dynamic field environments to resolve real-time regulation of plant physiology (solution tags: pillars 2 and 5 [single-cell/spatial, field-omics]; Figure 6).

Modeling complexity and interpretability

ML and DL models have demonstrated success in trait prediction and gene network inference; however, their “black-box” nature limits biological interpretability and scientific trust. In contrast,

mechanistic models—such as ordinary differential equation-based frameworks and Boolean networks—offer greater clarity but may oversimplify system complexity or struggle with scalability (Yasmeen et al., 2023). Hybrid modeling approaches that combine ML with rule-based or network-driven inference (e.g., knowledge-augmented neural networks) are emerging to balance predictive accuracy with interpretability (Ahmed et al., 2023). In parallel, explainable AI (XAI) frameworks are gaining momentum by enabling transparent predictions, feature relevance, and testable hypotheses. Despite these advances, most existing models lack generalizability across genotypes, developmental stages, and environmental conditions, limiting their utility in breeding pipelines and real-world stress scenarios (Danilevicz et al., 2023; Onoja, 2023; Sharma et al., 2024). There is an urgent need to develop biologically meaningful, interpretable, and context-aware models that bridge the gap between computational prediction and functional validation (solution tags: pillars 1 and 3 [hybrid models, XAI/causal]; Figure 6).

Limited translational pipeline to field applications

Although multi-omics and network analyses have identified numerous candidate genes, transcription factors, and stress

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regulators, only a small fraction have been functionally validated or deployed in crop improvement programs. Major barriers include the genetic complexity of quantitative traits, regulatory constraints on gene editing, limited technical tools for non-model crops, and unintended yield penalties associated with trait stacking (Roychowdhury et al., 2023; Yang et al., 2023; Mushtaq et al., 2025). In addition, disconnects among molecular biology, breeding, agronomy, and socioeconomic considerations often delay or impede translational progress. Participatory research models and co-design approaches involving farmers, breeders, and policymakers remain underutilized. Establishing a robust, interdisciplinary translational framework that links discovery science with breeding and field deployment is therefore critical to maximize the impact of plant systems biology (solution tags: pillars 5 and 6 [field-omics integration, participatory/open science]; Figure 6).

Underrepresentation of non-model crops

A disproportionate focus on *Arabidopsis*, rice, and maize has skewed systems biology resources toward a narrow subset of global crops. In contrast, climate-resilient and nutrient-rich species such as millets, pulses, legumes, and root/tuber crops remain severely understudied despite their ecological and economic importance (Rehman et al., 2023; Regon et al., 2024; Kundu et al., 2025a; Kumar et al., 2025b). Many of these crops lack high-quality genome assemblies, reference transcriptomes, robust annotation pipelines, or population-scale variation datasets (Cahais et al., 2012). The absence of comprehensive omics infrastructure and publicly accessible databases further limits their inclusion in comparative analyses and global predictive models. Targeted investments in genome sequencing, multi-omics resource development, and open-access infrastructure are urgently needed to extend systems biology beyond traditional model species. A conceptual framework outlining next-generation crop engineering challenges is illustrated in Figure 5 (solution tags: pillars 6 and 7 [inclusive open science; plant-microbiome-environment]; Figure 6).

STRATEGIC ROADMAP AND LONG-TERM VISION

Plant systems biology is poised at a transformative threshold, transitioning from descriptive omics profiling toward predictive, design-driven, and translational frameworks that will underpin the future of climate-resilient agriculture. While substantial technological and translational progress has been achieved in recent years, the next frontier lies in scaling these innovations into *dynamic, context-aware, and globally inclusive systems*. To fully realize this potential, *targeted advances* are required across multiple domains, including computational modeling, high-resolution multi-omics, digital agriculture, synthetic biology, and equitable access to data and analytical tools. This section outlines a *strategic vision and long-term roadmap* for next-generation plant systems biology, with priorities focused on bridging laboratory insights and field-level impact through integrative, transparent, and scalable solutions. Each of the preceding challenges directly maps onto the seven solution pillars presented below, ensuring a coherent transition from problem identification to strategic implementation.

1. *Dynamic multi-scale and context-aware modeling*: to simulate biological processes across hierarchical levels, from mo-

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lecular to phenotypic scales, future systems biology must integrate mechanistic modeling with ML and hybrid inference frameworks. Multi-scale models that integrate gene regulatory networks, metabolic fluxes, and environmental response modules enable real-time simulation of plant growth, development, and adaptation. These models should explicitly incorporate genotype $\times$ environment $\times$ management ($G \times E \times M$) interactions to inform breeding strategies and agronomic decision-making.

2. *High-resolution spatiotemporal omics*: expanding the application of single-cell as well as spatial transcriptomics and metabolomics across both model and non-model crops is essential for capturing cellular heterogeneity, developmental zonation, and tissue-specific stress responses. Integration of these high-resolution datasets with time-series measurements will facilitate dynamic modeling of developmental transitions, organogenesis, and stress adaptation at unprecedented spatial and temporal resolution.
3. *Explainable AI and causal inference*: although ML and DL approaches have substantially advanced pattern discovery, they often lack interpretability. Future efforts should emphasize explainable artificial intelligence (XAI), causal modeling (e.g., Bayesian networks and structural equation models), and biologically informed neural networks to ensure transparent, hypothesis-driven, and generalizable predictions. Together, these tools will empower researchers to uncover mechanistic insights and identify actionable intervention points for genome engineering and precision phenotyping.
4. *Digital twins and virtual crop systems*: next-generation crop modeling will be driven by “digital twins”—computational replicas of real-world plants that simulate development, physiology, and productivity under variable environmental conditions. These virtual systems will integrate multi-omics data, genotype information, and agronomic variables to test hypotheses, predict trait performance, and guide breeding strategies. Digital twins hold strong potential for precision agriculture, genotype-by-environment ($G \times E$) analyses, and rapid ideotype design under climate uncertainty.
5. *Field-omics-phenomics integration*: to enhance translational impact, molecular data must be contextualized with field-based phenotyping and environmental inputs. Combining UAV-based imaging, Internet of Things (IoT) sensors, chlorophyll fluorescence measurements, and root imaging platforms with transcriptomic, metabolomic, and proteomic profiles will enable real-time crop monitoring and predictive diagnostics. Such integrated frameworks will support dynamic agronomic decision-making and early detection of stress signals under field conditions.
6. *Participatory, inclusive, and open science*: meaningful global progress in plant systems biology requires equitable access to data resources, analytical tools, and training opportunities. Expanding systems biology research to underrepresented crops and regions—particularly in the Global South—will necessitate targeted funding, sustained capacity building, open-access databases, and FAIR-compliant data infrastructures. Strengthening public-private partnerships, community-oriented breeding platforms, and participatory research models will help ensure

Grand challenges limiting the translational potential of plant systems biology

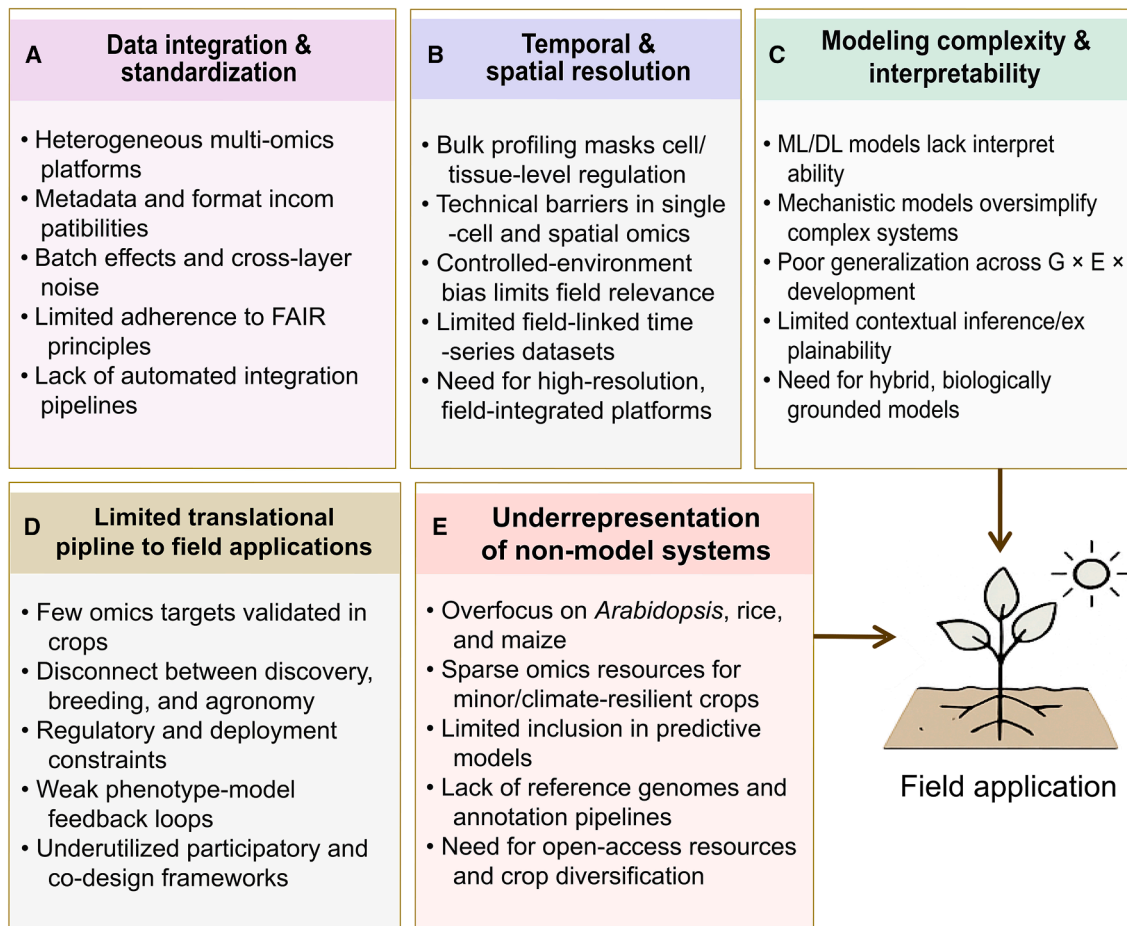


Figure 5. Grand challenges limiting the translational potential of plant systems biology.

This conceptual framework outlines five interconnected domains that constrain the transition from multi-omics discovery to field-ready agricultural innovation.

(A) *Data integration and standardization*: heterogeneous platforms, inconsistent metadata, batch effects, and incomplete implementation of FAIR principles hinder cross-scale data synthesis and reproducible network modeling.

(B) *Temporal and spatial resolution limitations*: bulk profiling obscures cellular heterogeneity, while technical constraints in single-cell and spatial omics, together with the scarcity of field-linked time-series datasets, limit the capture of dynamic regulatory processes.

(C) *Modeling complexity and interpretability*: deep-learning models often lack transparency, mechanistic models may oversimplify biological systems, and limited generalizability across genotype $\times$ environment $\times$ development contexts reduces predictive robustness.

(D) *Translational pipeline gaps*: few omics-derived targets advance to validated crop traits due to regulatory constraints, insufficient phenotype-model feedback, and weak coordination among discovery research, breeding programs, and agronomic practice.

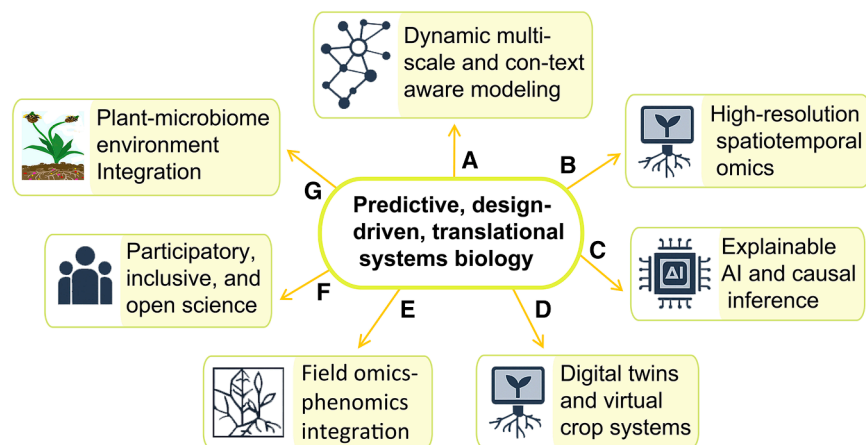
(E) *Underrepresentation of non-model systems*: the predominant focus on *Arabidopsis*, rice, and maize leaves minor and climate-resilient crops lacking genomic resources, annotation pipelines, and integration into predictive frameworks. Collectively, these challenges underscore the need for harmonized data infrastructures, high-resolution spatiotemporal omics, interpretable and generalizable models, and inclusive, field-integrated translational pipelines to accelerate predictive, climate-resilient agriculture.

that cutting-edge innovations are effectively disseminated to farmers and end-users.

7. *Plant-microbiome-environment integration*: this framework expands plant systems biology to encompass tripartite interactions among the host plant, its microbiome (including rhizosphere and endosphere communities), and the surrounding abiotic environment. Such integration enables mechanistic modeling of nutrient cycling, root exudate-microbe feedbacks, stress resilience, and plant-soil health dynamics. By incorporating meta-genomics, meta-transcriptomics, and environmental metadata, this

approach supports ecosystem-level trait optimization and the development of climate-smart, microbiome-informed crop management strategies.

By addressing these frontiers, plant systems biology can evolve from a fragmented, data-rich discipline into a coherent, predictive, and application-oriented science, as illustrated in Figure 6. The integration of multi-omics, explainable modeling, real-time phenotyping, and inclusive knowledge-sharing will empower researchers and farmers alike to co-develop resilient cropping systems. Grounded in biological complexity yet guided by



Vision and future roadmap for plant systems biology

(E) *Field-omics-phenomics integration*, merging molecular, physiological, and imaging data to support real-time monitoring and decision-making. (F and G) (F) *Participatory and open science frameworks* that promote equitable data access and FAIR-compliant collaboration (G) *Plant-microbiome-environment integration* that captures dynamic biotic-abiotic feedbacks underlying stress resilience. Together, these pillars define a holistic, adaptive, and data-intelligent framework that advances plant systems biology toward sustainable, climate-smart agriculture.

data-driven insights, systems-informed agriculture will play a central role in advancing food security, environmental sustainability, and climate adaptation in the 21st century.

Concluding remarks

The convergence of high-throughput multi-omics technologies with advanced computational and mechanistic modeling has re-defined the conceptual and methodological frontiers of plant biology. Systems biology now provides a rigorous and integrative framework for decoding the complex regulatory architectures underlying plant development, stress adaptation, and trait plasticity. By integrating genomics, transcriptomics, proteomics, metabolomics, epigenomics, and phenomics within predictive and mechanistic models, this discipline reveals emergent properties and dynamic cross-scale interactions that cannot be resolved by reductionist approaches. Integrative frameworks that combine network biology, ML, and dynamic simulations have transformed our understanding of gene regulation, hormonal crosstalk, metabolic fluxes, and phenotypic outcomes. These insights are increasingly being translated into actionable strategies for precision genome editing, synthetic circuit design, and predictive breeding, establishing the foundation of a data-driven crop design paradigm. Nonetheless, critical challenges remain, including scalable multi-omics integration, improved spatiotemporal and single-cell resolution, biologically interpretable and generalizable models, and rigorous field validation under realistic agroecological conditions. Addressing these limitations will require next-generation strategies that integrate explainable AI, spatial and single-cell omics, digital twin modeling, and participatory translational pipelines. Looking ahead, plant systems biology is emerging not merely as a technological toolkit but as a foundational discipline that bridges molecular complexity with ecological and agronomic relevance. Its successful implementation will be pivotal for developing resilient, resource-efficient, and climate-adaptive crops, thereby aligning plant science with the grand challenges of sustainable agriculture, food security, and environmental stewardship. As this field advances from data accumulation toward predictive design, plant systems biology

Figure 6. Vision and future roadmap for next-generation plant systems biology.

This schematic outlines seven innovation pillars shaping the transformation of plant systems biology from a descriptive discipline to predictive, design-driven, and translational science. At the core is *predictive systems biology*, supported by the following components: (A) *Dynamic multi-scale modeling* that links molecular regulation, development, and environmental responses through hybrid mechanistic-machine-learning frameworks. (B) *High-resolution spatiotemporal omics* that resolve cellular heterogeneity through single-cell and spatial profiling. (C) *Explainable AI and causal inference* approaches that enhance transparency and biological interpretability. (D) *Digital twins and virtual crop systems* that simulate genotype $\times$ environment $\times$ management interactions.

is poised to transform the future of integrative and climate-smart crop research.

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AUTHOR CONTRIBUTIONS

B.K.K. conceived the study, designed the conceptual framework, developed the analytical pipelines, wrote the original draft, and revised the manuscript. B.T. co-wrote and revised the manuscript and supervised the research.

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